Remarks

Claims 1, 2, 4-6, 8-21 and 25-32 are pending. Claims 1, 2, 4-6, 8-21 and 25-32 are rejected. Claim 1 is amended herein. New claims 33-34 are added herein. Support for new claims 33-34 can be found throughout the specification, such as, but not limited to, page 32 and 45-47.

Applicants believe no new matter is added herein. Reconsideration of the subject application is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6, 8-21 and 27-32 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Office action contends that the steps of the claimed method are unclear as they refer to preventing an opportunistic infection in an immunocompromised subject. Applicants respectfully disagree. However, in order to advance prosecution, claim 1 is amended herein to clarify that the immunocompromised subject is infected with the opportunistic infection, in order to clarify that the claimed methods are directed to treatment of opportunistic infections. Claims 2, 4-6, 8-21 and 27-32 depend from claim 1. Applicants submit that the amendment of claim 1 renders the rejection moot.

Claim 26 is rejected under 35 U.S.C. § 112, second paragraph as being improperly dependent. Claim 26 is amended herein to depend from claim 1, rendering the rejection moot.

Rejections Under 35 U.S.C. § 102(b)

Claims 1, 8-17 and 21 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 6,977,245 (Klinman et al.). Klinman et al. was published on December 20, 2005. The present application was filed on December 17, 2003, and is entitled to the benefit of a provisional application filed on December 18, 2002. Thus, Klinman et al. is not available as a reference under 35 U.S.C. § 102(b).

Klinman et al. was also published as U.S. Patent Application No. 2003/0060440 on March 27, 2003. The present application was filed on September 19, 2003, and claims the

benefit of U.S. Provisional Application No. 60/411,944. Thus, U.S. Patent Application No. 2003/0060440 is also not available as a reference under 35 U.S.C. § 102(b).

Klinman et al. is a continuation in part of U.S. Application No. 09/958,713. If the Examiner intended to issue a rejection under 35 U.S.C. § 102(e) the Applicants request that the Examiner enumerate which sections of the priority application are being used for the present rejection.

MPEP §2131 sets forth that "to anticipate a claim, the reference must teach every element of a claim." The Office action acknowledges on page 4 of the Office action that Klinman et al. "*does not describe any secondary infections* (see page 4 of the Office action, lines 6-7). Thus, Klinman et al. simply cannot anticipate the claimed methods.

The Office action refers to paragraph 47 of Klinman et al. as teaching use of D ODNs (those ODNS specified in claim 1) in an immunocompromised subject. The Applicants contacted the Examiner for clarification, since Klinman et al. as published (or as available through PAIR) does not include paragraph numbers. The Examiner informed the undersigned that paragraph 47 of Klinman et al. corresponded to the paragraph found at column 7, lines 48-59 of Klinman et al..

This paragraph appears in the section of "Terms" provided for review of the document. For the Examiner's convenience, the paragraph is copied below:

> **Immune system deficiency:** A disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response. Immune system deficiencies include those diseases or disorders in which the immune system is not functioning at normal capacity, or in which it would be useful to boost the immune system response. In one specific, non-limiting example, a subject with an immune system deficiency has a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small cell), ovary, breast, prostate, colon, as well as other carcinomas and sarcomas).

Clearly this paragraph only defines an immune system deficiency. This paragraph does not disclose any agents of use in immunocompromised subjects, let alone to treat secondary infections. Indeed, the susceptibility of subjects with an immune system deficiency to secondary infections is not discussed in Klinman et al., nor is the treatment of these subjects. In addition,

Klinman et al. does not describe evaluating an immune response to a secondary infection in an immunocompromised subject.

Thus, in addition to not being available as prior art under 35 U.S.C. § 102(b), Klinman et al. simply fails to anticipate the claimed methods.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4-6, 9-22 and 25-32 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Klinman et al. in view of Fraternale et al. Applicants respectfully disagree with this rejection.

Klinman et al. is discussed above. Klinman et al. teaches D type ODNs, and discloses that D type ODNs are of use to treat infections. Klinman et al. does not suggest, nor render obvious, the use of D type ODNs to treat an immunocompromised subject infected with a secondary infection, nor does Klinman et al. teach evaluating an immune response to a secondary infection in an immunocompromised subject following treatment with a D ODN. The Office action further acknowledges that Klinman et al. does not teach treatment with HAART or azidothymidine (AZT).

Fraternale et al. discuss the use of combinations of protease and reverse transcriptase inhibitors in mice infected with LP-BM5, which produces severe immunodeficiency. Fraternale et al. use mice infected with LP-BM5 to select the most effective way to administer fludarabine, a lympholytic drug, to inhibit disease progression. Fraternale et al. evaluate the efficacy and toxicity of a combination of fludarabine and AZT (an antiviral drug). Fraternale et al. conclude that sequential administration of fludarabine (a lympholytic drug) and AZT (an anti-viral agent) is most effective in reducing spleen and lymph node weights to normal values and decreasing LP-BM5 viral content. Fraternale et al. does not describe the effect of any therapeutic intervention on secondary infections.

The Office action alleges that one of skill in the art would be motivated to use D ODNs, and would have a reasonable expectation of success, based on the teachings of Klinman et al. and Fraternale et al. This is simply incorrect.

I. Klinman et al. Is Not Available As Prior Art under 35 U.S.C. § 102(b)

The Office action states that Klinman et al. is available as prior art under 35 U.S.C. § 102(b). This is not correct. The U.S. PTO has not provided sufficient information to determine why Klinman et al. can be properly cited against the present application under 35 U.S.C. § 102(b) or any other subsection of § 102.

Fraternale et al. does not describe the use of any oligodeoxynucleotides (ODN), let alone D ODN. Moreover, Fraternale et al. does not describe the treatment of secondary infections. Thus, Fraternale et al. alone does not render the claimed methods obvious.

However, even if one were to combine the teachings of Klinman et al. with Fraternale et al., the claimed methods are not obvious. Thus, in the interest of advancing prosecution, the combination of references will be addressed.

II. There is No Reason for One of Skill in the Art to Combine Fraternale et al. and Klinman et al.

Klinman et al. teaches the use of immunostimulatory molecules, namely D ODNs, to treat infections, autoimmune diseases and cancer (see column 17, lines 42-66). Klinman et al. also teach that D ODNs can be used to enhance the efficacy of vaccines or to treat infections, including viral infections. The D ODNs described by Klinman et al. are effective as adjuvants.

This is very different from the teachings of Fraternale et al. who discloses that fludarabine, a lympholytic drug, can be used to treat HIV. Fraternale et al. teach that lympholytic drugs are of use to eliminate (kill) HIV infected cells. Once HIV is eradicated from the long-lived compartments by the lysis of lymphocytes, antiretroviral nucleoside analogs are administered to protect non-infected cells (see page 210, first column).

Fraternale et al. teaches that it is advantageous to kill infected lymphocytes. Thus, Fraternale et al. inherently *teaches away* from the use of agents that are immunostimulatory, such

as D ODN. Indeed one of skill in the art would expect an immunostimulatory agent, such as a D ODN, to counteract the effects of fludarabine.

As set forth in MPEP § 2145, a "prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness." As Fraternale et al. teaches the use of lympholytic agent, and Klinman et al. teaches immunostimulatory agents, one of skill in the art would not be motivated to combine the teachings of Klinman et al. with Fraternale et al.

III. There are Substantial Differences Between the Cited Prior Art and the Presently Claimed Methods

The Office action also does not ascertain the differences in the cited prior art from the presently claimed methods, as required by MPEP § 2141. The presently claimed methods are directed to the use of D ODN for the treatment of opportunistic infections in immunocompromised subjects. Neither Klinman et al. nor Fraternale et al. teach the treatment of an opportunistic infection in an immunocompromised subject, nor do they teach assessment of a secondary infection.

Thus, there are distinct differences between the cited prior art and the presently claimed methods. The prior art does not teach all of the elements of the presently claimed methods, and one of skill in the art could not arrive at the presently claimed methods based on the general teachings of the cited prior art.

IV. Declaration Evidence Documents One of Skill in the Art Could Not Predict the Effectiveness of the Claimed Methods Based on the Cited Prior Art

If one accepts the Examiner's assertions at face value (and the Applicant's do not believe that these assertions are correct), one of skill in the art, reading Klinman et al., would try to administer D ODN to immunocompromised subjects. A Declaration of Daniela Verthelyi under 37 C.F.R. § 1.132 was submitted on June 5, 2008 (hereinafter the "Declaration'). This Declaration described experiments conducted with D ODN on peripheral blood mononuclear cells (PBMC) isolated from immunocompromised subjects and healthy subjects (see page 2 of the Declaration). PBMC were exposed to D ODN using the presently claimed methods, K ODN (a different type of immunostimulatory ODN), and control ODN. The sequences of the ODNs

used in the experiments are provided in the Declaration, and are also set forth in the specification on page 45.

PBMC from HIV infected and healthy subjects responded similarly to K type ODN (see Figure 1 of the Declaration), suggesting that B cells and monocytes retained their ability to respond to this form of immune stimulation. *However, although D type ODN induced a significant increase in cytokine secretion by cells from both donor populations ($p< 0.001$), the IFNγ response of healthy controls significantly exceeded that of HIV-infected subjects* ($p<0.05$ and $p<0.001$, respectively, Figure 1). The reduced responsiveness to D ODN correlated directly with the number of $CD4^+$T cells among the HIV infected donors ($p<0.01$) and inversely with their viral load ($p<0.05$). On page 3 of the Declaration, data is presented documenting that D ODN were less effective at inducing the maturation of dendritic cells in PBMC from HIV infected individuals than normal donors. On page 5 of the Declaration, it is disclosed that SIV-infected macaques were treated with D35 (SEQ ID NO: 177), there was no change in the number of CD4 or CD8 cells. The Declaration documents that D ODNs were ineffective at producing cytokines, increasing the number of T cells, decreasing viral load, or inducing the maturation of dendritic cells in immunocomprosed subjects who were not infected with a secondary infection. Thus, one of skill in the art simply could not have arrived at the presently claimed methods based on the teachings of Klinman et al. and Fraternale et al. *Thus, contrary to the assertions made in the Office action, using the teachings of Klinman et al. and Fraternale et al., one of skill in the art would not simply ascertain that D ODNs were effective in immunocompromised subject.* There is no reasonable expectation of success (or scientific evidence to support) that this combination would be effective.

V. Declaration Evidence of Unexpectedly Superior Results Overcomes a Prima Facie Case of Obviousness

In addition, the Declaration provides evidence of the unexpectedly superior result obtained using D ODN. The Declaration on pages 4-5 describes the results obtained when D ODNs were evaluated in an art-accepted macaque model of HIV. Macaques that had been infected >12 months earlier with SIV Mac239 and had viral loads ranging from 0.3-28 $x10^6$ copies/ml were used. The animals were stratified based on viral load and then challenged with *L. major* metacyclic promastigotes (MHOM/IL/80/Friedlin), which is a secondary infection.

Healthy macaques challenged with L. major develop cutaneous lesions characterized by erythema, induration and ulceration that peaked 25 days after challenge and resolved within 50 days (see the Declaration, Fig. 3A). Due to their immunosuppressed state, untreated macaques developed severe progressive cutaneous lesions that did not resolve. The severity of *Leishmania* infection in SIV-infected animals treated with K ODN (another type of immunostimulatory ODN) was not significantly different from that of the controls.

In contrast, SIV-infected macaques treated with D ODN developed significantly smaller lesions, and their infection did not progress over time (see Figure 3A of the Declaration) as compared to controls. The animals were euthanized on day 56, and their parasite burden measured. SIV-infected monkeys treated with D ODN had a *35-fold reduction* in total parasite burden at the lesion site compared to SIV infected animals treated with control ODN or saline (see the Declaration Fig. 3B, $p<0.001$). This unexpectedly superior result simply could not have been predicted based on the teachings of Klinman et al. and/or Fraternale et al.

The showing of unexpectedly superior results overcomes any *prima facie* case of obviousness.

VI. Summary

The above arguments clearly demonstrate that the claimed methods are not obvious over Klinman et al. and/or Fraternale et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe the pending claims are in condition for allowance, which action is requested. If for any reason the rejection is maintained, or if any new rejections are asserted, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview. Applicants have made every effort to comply with the Examiner's suggestions and have addressed all of the rejections based on the prior art. Thus, if any new prior art is cited, Applicants believe that it would be inappropriate to issue a final Office action.

It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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